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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/727,461	12/04/2003	John D. Shaughnessy	D6485	6235

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EXAMINER	
FETTEROLF, BRANDON J	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 01/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/727,461	SHAUGHNESSY, JOHN D.	
	Examiner	Art Unit	
	Brandon J. Fetterolf, PhD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 October 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15,18 and 19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15 and 18-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Shaughnessy, J.D.

Response to the Amendment

The Amendment filed on 10/31/2005 in response to the previous Non-Final Office Action (08/10/2005) is acknowledged and has been entered.

Claims 15 and 18-19 are currently pending and under consideration.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Rejections Maintained:

Claims 15 and 18-19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The instant claims read on a method of determining the risk of developing bone disease in a test individual comprising examining the expression level of a WNT signaling antagonist, wherein increased expression of the antagonist compared to that in a normal individual indicates that said test individual has the risk of developing bone disease. Claims must be interpreted as broadly as their terms reasonably allow. Thus, the claims read on a method of determining the risk of a bone disease, which encompasses bone diseases that have yet to form in the mammal.

However, the instant claims are not commensurate with the enablement of the instant disclosure, because practice of the claimed invention would require undue experimentation by an artisan of ordinary skill in the art. The instant specification is not enabling for claims drawn to determining the risk of developing any and/or all bone disease in a test individual comprising examining the expression level of a WNT signaling antagonist, wherein increased expression of the antagonist compared to that in a normal individual indicates that said test individual has the risk of developing bone disease. The specification teaches that 174 patients with "newly" diagnosed multiple myeloma, 16 patients with monoclonal gammopathy of undetermined significance, 9 with Waldenstroms macroglobulinemia, and 45 normal persons were studied in the present invention (page 27, lines 10-16). The specification further provides (page 35, Example 8) an analysis of the results obtained from 173 patients with myeloma, wherein the DKK1 signal for patients with 1 + MRI and no x-ray lesion differ significantly compared to patients with no MRI and no x-ray lesions, but does not differ significantly compared to patients with 1 + MRI and 1 + x-ray. Moreover, the specification teaches (page 9, Example 9) a correlation between global gene expression of DKK-1 and lytic bone lesions in multiple myeloma. Thus, while the specification clearly teaches a diagnosis of bone disease in a multiple myeloma patient comprising comparing the level of DKK-1 expression in an individual with multiple myeloma compared to a "normal" individual, the specification appears to be silent on how to interpret this as a method of determining the risk of developing any and/or all bone disease.

In the instant case, the closest prior art, McCarthy (WO 0052047, 2000), to the claimed invention teaches human dickkopf-related proteins (referred to herein as DKK) and uses thereof, wherein one activity associated with the DKK family of proteins is the

modulation, e.g., antagonism, of the activity of the Wnt family of secreted proteins (page 23, lines 16-18). Specifically, the WO document teaches a method of diagnosing a disease or disorder associated with aberrant expression or activity of DKK (abstract). While McCarthy contemplates determining the risk of developing a disease associated with aberrant expression or activity of a DKK protein (page 96, lines 14-16), there does not appear to be any demonstration that the DKK family of proteins can be used to determine risk.

Those of skill in the art recognize that reasonable guidance with respect to assessing the risk of any cancer relies on quantitative analysis from defined populations which have been successfully pre-screened and monitored over some period of time prior to the disposition of cancer. The majority of the initial data may be derived from widespread genetic analysis, cancer clusters, or family histories. For example, Chappuis et al. (Cancer Treat Res. 2002; 107: 29-59) discloses an analysis of risk assessment and the importance of genetic testing in ovarian cancer. Specifically, Chappuis et al. teaches that in ovarian cancer, family history is one of the strongest known risk factors, wherein approximately 5 to 13% of all ovarian cancer cases are caused by the inheritance of cancer predisposing genes with an autosomal pattern of transmission (abstract). In addition to genetic factors, McLaughlin et al. (Tannock, I.F. and Hill, R.P., The Basic Science of Oncology, Chapter 2, (3rd Ed., 1998)) teaches that there are a plethora of environmental factors ar which are also determinants for cancer risk in a population. Some environmental factors disclosed by McLaughlin et al. include exposure to tobacco products, dietary factors, alcohol and occupational exposure (page 16). In the instant case, the specification is devoid of any models or experimental analysis that reasonably suggests that the claimed method would predictably determine the risk of the development of a bone disease in an individual. This, combined with the state of the art of preventing cancer, suggests that undue experimentation would be required to practice the invention as broadly claimed.

In response to the rejection, Applicants contend that the claim 15 reads on "risk of developing a bone disease" and not risk of developing cancer as referred to in the teachings of Chappuis et al. and McLaughlin et al.. As such, Applicants submit that the claim recites a logical conclusion inferred from experimental analysis. For example, Applicants assert that the prior art has identified that gain of function mutations in LRP-5 is linked to a high bone mass phenotype and that DKK-1 inhibition is defective in the presence of such mutations

which results in increased WNT signaling. Thus, Applicants assert that the increase in WNT signaling mediated by decrease in DKK-1 inhibition results in higher osteoblast activity leading to high bone mass. Furthermore, Applicants argue that it has been demonstrated that targeted disruption of LRP-5 gene, in a mice model, results in low bone mass phenotype (pgs. 19-23). Applicants further contend that one can logically conclude from above, that if the level of DKK-1 expression increases then there would be low osteoblast (bone formation) activity due to a concomitant decrease in WNT signaling; and therefore, an individual exhibiting higher levels of DKK-1 protein would be at a high risk of developing a bone disese characterized by bone loss as a result of low osteoblast activity that is mediated via the WNT signaling pathway. Additionally, Applicants submit that example 17 provides important data on the role of DKK-1 in osteoblast differentiation, wherein DKK-1 was shown to inhibit osteoblast activity. Also, Applicants contend that examples 8 and 9 adequately demonstrate higher up regulation of DKK-1 in individuals with multiple myeloma accompanied by lytic lesions as compared to individuals with no bone lesions such that it is fair to conclude that individuals with up regulation of DKK-1 are at risk of developing a bone disease characterized by bone loss. Therefore, Applicants argue that establishing the presence of a specific risk factor such as over expression of DKK-1 in individuals provides suitable clinical guidelines to delay if not eliminate onset of such bone related disease.

These arguments have been carefully considered, but are not found persuasive.

In response to Applicants contention that the claim 15 reads on "risk of developing a bone disease" and not risk of developing cancer as referred to in the teachings of Chappuis et al. and McLaughlin et al., the Examiner recognizes that the instantly pending claims read on a risk of developing a bone disease and not a risk of developing cancer. However, reasonable guidance with respect to assessing the risk of any disease and/or disorder relies on the quantitative analysis of a defined population which have been successfully pre-screened and monitored over some period of time prior to the disposition of the disease or disorder, wherein initial data may be derived from widespread genetic analysis or family histories. While both Chappuis et al. and McLaughlin et al. teach the importance of family history and environmental factors for cancer, the same "risk factors" are important when assessing the risk of a bone disease as exemplified by Stevenson et al. (BMJ 1989; 298: 924-

928) and Soroko et al. (J. Bone Miner. Res. 1994; 9: 761-769). Moreover, although Applicants contend that one would conclude in view of the prior art and Examples 17, 8 and 9 of the specification, that DKK-1 expression could be used to determine the risk of a bone disease characterized by bone loss, the Examiner recognizes that attorney's arguments cannot take the place of evidence. As such, objective evidence must be factually supported by an appropriate affidavit. Therefore, because the specification only appears to suggest diagnosis of bone disease in a multiple myeloma patient by comparing the level of DKK-1 expression in an individual with multiple myeloma compared to a "normal" individual and is silent on how to interpret this as a method of determining the risk of developing any and/or all bone disease, undue experimentation would be required to practice the invention as broadly claimed.

Therefore, NO claim is allowed

All other rejections and/or objections are withdrawn in view of applicant's amendments and arguments there to.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-

272-2919. The examiner can normally be reached on Monday through Friday from 8:30 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeff Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Brandon J Fetterolf, PhD
Examiner
Art Unit 1642

BF

JEFFREY SIEW
SUPERVISORY PATENT EXAMINER
1/9/05